An efficient improved synthesis of carvedilol, 
via 2-(2-methoxyphenoxy)ethyl 
4-methylbenzenesulfonate intermediate

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A facile synthesis of Carvedilol via a key 2-(2-methoxyphenoxy)ethyl 4-methylbenzenesulfonate intermediate is described and this approach avoids the formation of bis side product (impurity-B) due to weak basic conditions and also operationally suitable for industrial application.

Keywords: Carvedilol, impurity-B, 2-(2-methoxyphenoxy)ethyl 4-methylbenzenesulfonate, β-amino alcohol, β-adrenergic blocking agent

Carvedilol (Figure 1) is a non-selective β-adrenergic blocking agent with α1-blocking activity. β-Adrenergic blocking agents14, mostly comprising of β-amino alcohols, are of pharmaceutical interest and have received major attention due to their utility in the management of cardiovascular disorders5 including hypertension, angina pectoris, cardiac arrhythmias and other disorders related to the sympathetic nervous system.

Several syntheses of Carvedilol are reported. The innovator, Boehringer Mannheim, approach for the synthesis of Carvedilol is the opening of oxirane ring of 4-(oxiran-2-yl methoxy)-9H-carbazole5, with 2-(2-methoxyphenoxy)ethanamine8 (Scheme I). In this reaction, bis side product, also known as impurity-B (Figure 1) is formed about 30-40% which on workup and isolation is reduced to 10-15%. It is very difficult to remove this impurity by any purification methods once it is formed in the reaction. Hence it is essential to control the formation of this impurity in the reaction itself. In order to avoid the formation of this impurity in the reaction, several attempts also made reported in the literature9,11. Various parameters like solvent, temperature, reaction time and mode of addition have been studied to avoid the formation of the same but none of these parameters played a significant role.

Results and Discussion
As part of our ongoing research on process development of Carvedilol, herein we had developed new synthetic approach for the synthesis of Carvedilol 5 with high purity by eliminating the side product. This approach follows the replacement of tosyl group in 2-(2-methoxyphenoxy) ethyl-4-methylbenzenesulfonate 14 (Scheme II) with β-amino alcohol intermediate 9 (Scheme II) under mild basic medium afforded Carvedilol 5 (Scheme II). The reaction of 2-methoxyphenol 10, with 2-chloroethanol 11 in a strong base such as sodium hydroxide in water medium gave 2-(2-methoxyphenoxy) ethanol 12. Condensation of compound 12 with 4-methylbenzene-1-sulfonyl chloride 13 in a strong basic medium such as sodium hydroxide in toluene resulted in 2-(2-methoxyphenoxy)ethyl 4-methylbenzenesulfonate 14. Reaction on compound 3 with conc HCl gave 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol12,6, which on further condensed with potassium phthalimide 7 resulted 2-(3-(9H-carbazol-4-yloxy)-2-hydroxypropyl)isoindoline-1,3-dione 8. The obtained compound 8 was treated with mono methyl amine yielded the β-amino alcohol intermediate13,9.

Experimental Section
Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One). 1H spectra were recorded on Varian 300 and 400 MHz spectrometers using CDCl3, DMSO-d6 as solvents, and tetra methyl silane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turbo ion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up. The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring.
Synthesis of 1-((9H-Carbazol-5-yloxy)-3-chloropropan-2-ol, 6: To a stirred solution of compound 3 (60 g, 0.250 mol) in methanol (600 mL) at 0-5°C was added concentrated HCl (15 mL) slowly drop-wise over a period of 30-45 min at the same temperature. Reaction mass allowed to 25-30°C for 5-6 hr then distilled off methanol completely under vacuum to get the material as colorless residue. Residue was recrystallized by 10% methanol in toluene at 25-30°C to get pure compound 6 as off white crystalline powder (43.8 g, Yield: 63.5%). IR (KBr): 3394 (-OH), 725 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 11.2 (s, 1H, -NH), 8.2 (d, 1H, \(J = 7.7\),-aromatic), 7.4 (d, 1H, \(J = 8.0\),-aromatic), 7.3 (m, 2H,-aromatic), 7.1 (m, 2H,-aromatic), 6.7 (d, 1H, \(J = 7.8\),-aromatic), 4.2 (m, 3H,-CH\(_2\) and-CH); MS: \(m/z\) (M) 275.

Preparation of 2-(3-(9H-carbazol-5-yloxy)-2-hydroxy propyl)isoindoline-1, 3-dione, 8: To a mixture of compound 6 (40 g, 0.145 mol), K\(_2\)CO\(_3\) (32.22 g, 0.174 mol) in DMF (120 mL) was added potassium pthaliamide 7 (32.22 g, 0.174 mol). The reaction mass was heated for 2 hr at 90-95°C then cooled to 25-30°C, added water (200 mL), ethyl acetate (200 mL) and then stirred for 10 min. The ethyl acetate layer was separated from aqueous layer, dried over sodium sulfate and the solvent was removed under reduced pressure to get required compound 8 as an off white crystalline powder (45.9 g, Yield: 82.0%). IR (KBr): 3282 (-OH), 3057 (-aromatic), 1698 cm\(^{-1}\) (-C=O); \(^1\)H NMR (DMSO-\(d_6\), 400 MHz): \(\delta\) 11.2 (s, 1H,-NH); 8.3 (d, 1H, \(J = 7.2\),-carbazole), 7.9 (m, 4H, -aromatic), 7.5 (d, 1H, \(J = 7.4\),-carbazole), 7.3 (m, 2H, -carbazole), 7.1 (m, 2H, -carbazole), 6.7 (d, 1H, \(J = 6.8\),-carbazole), 5.5 (s, 1H, -OH), 4.4 (m, 1H, -CH), 4.2 (d, 2H,-CH\(_2\)), 3.9 (m, 2H,-CH\(_2\)); MS: \(m/z\) (M+1) 387.2.

Preparation of 1-(9H-carbazol-4-yloxy)-3-amino-propan-2-ol, 9: To a solution of 250 mL 40% aq. monomethyl amine and compound 8 (40.0g, 0.103 mol) was stirred at 80°C for 2 hr. After completion of the reaction, the mass was cooled to 25-30°C and adjusted its pH to 2.0-2.5 with HCl. The reaction mass was washed with DCM (100 mL) and the resultant aqueous layer pH was adjusted to 12-13 with 50% aq. sodium hydroxide solution. The product was extracted with 250 mL of toluene and concentrated under reduced pressure to provide 1-(9H-carbazol-4-yloxy)-3-aminopropan-2-ol, 9 as a white solid (12.4 g, Yield: 47.2%). IR (KBr): 3398 (-NH\(_2\)), 2835 cm\(^{-1}\) (-OCH\(_3\)); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 11.3 (s, 1H,-NH), 8.16 (d, 1H, \(J = 6.8\),-aromatic), 7.5 (d, 1H, \(J = 6.6\),-aromatic), 7.3 (m, 2H,-aromatic), 7.1 (m, 2H,-aromatic), 6.8 (d, 1H, \(J = 7.8\),-aromatic), 5.1 (s, 1H,-OH), 4.2 (m, 3H,-CH\(_2\)-OCH\(_3\)), 2.8 (m, 2H,-CH\(_2\)-NH\(_2\)); MS: \(m/z\) (M+1) 257.2. Anal. Calcd for C\(_{15}\)H\(_{16}\)N\(_2\)O\(_2\) (256.3): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.25; H, 6.31; N, 10.95%.
Preparation of 2-(2-methoxyphenoxy)ethanol, 12: To a solution of 10 (50.0 g, 0.402 mol) in water (200 mL) added TBAB (3.5 g, 0.01 mol) and sodium hydroxide (48.3 g, 1.208 mol) then stirred together for 15 min at 30°C. To this mixture, added 2-chloroethanol 11 (38.9 g, 0.483 mol) at RT and stirred for 2 hr at 70°C for completion of the reaction. The reaction mixture was cooled to RT and extracted the product with toluene (200 mL). The organic layer was concentrated under reduced pressure to afford the title compound 12 (62.3 g, yield: 92.0%). IR (KBr): 3390 (–OH), 2838 cm\(^{-1}\) (–OCH\(_3\)); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 6.95 (m, 2H, –aromatic), 6.85 (m, 2H, –aromatic), 4.8 (s, 1H, –OH), 3.95 (m, 2H, –OCH\(_2\)), 3.75 (s, 3H, –OCH\(_3\)), 3.7 (m, 2H, –CH\(_2\)); MS: \(m/z\) (M) 168.

Anal. Calcd for C\(_9\)H\(_{12}\)O\(_3\) (168.19): C, 64.27; H, 7.17; O, 28.52 %.

Preparation of 2-(2-methoxyphenoxy)ethyl 4-methylbenzenesulfonate, 14: A mixture of 12 (50 g, 0.297 mol) in toluene (200 mL) was added sodium hydroxide (14.2 g, 0.356 mol) and stirred together for 10 min at 25-30°C. Added 4-methylbenzene-1-sulfonyl chloride (13) (68 g, 0.356 mol) slowly portion wise for 20-30 min and the reaction mass was stirred for 2 hr at 25-30°C. Added water (200 mL) to reaction mass and separated organic layer then it was concentrated under reduced pressure to get the desired compound 14 light brown color residue (82.6 g, yield: 86.2%). IR (KBr): 3064 (-CH aromatic), 2838 cm\(^{-1}\) (–OCH\(_3\)); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)/TMS): \(\delta\) 7.8 (m, 2H, –tosyl); 7.5 (m, 2H, –tosyl), 6.9 (m, 4H, –aromatic), 4.3 (m, 2H, –OCH\(_2\)), 4.1 (m, 2H, –CH\(_2\)), 3.7 (s, 3H, –OCH\(_3\)), 2.4 (s, 3H, –CH\(_3\)); MS: \(m/z\) (M+1) 323.


Preparation of 1-(9H-carbazol-4-yl)-3-(2-(2-methoxyphenoxy)ethylamino)propan-2-ol, 5 (Carvedilol): To a mixture of 14 (5 g, 0.019 mol), K\(_2\)HPO\(_4\) (6.79 g, 0.039 mol) TEBAC (0.2 g, 0.0001 mol) in toluene (25 mL) was added compound 9.
(7.5g, 0.023 mol) then the mixture was refluxed for 5 hr. The reaction mixture was cooled to RT and added water (30 mL). Separated the organic layer from aqueous layer and dried over anhydrous sodium sulfate then the solvent was removed under reduced pressure to get gummy residue material. The obtained residue was agitated with MTBE (20 mL) for three hours to get target product as white color solid (5.6 g, Yield: 92.5%). IR (KBr): 3344 cm$^{-1}$ (-OH); $^1$H NMR (CDCl$_3$, 400 MHz): δ11.3 (s, -NH, -carbazole), 8.1 (s, 1H, -carbazole), 7.4 (m, 2H, -Ar-H), 7.3 (d, 1H, $J$ = 2.6, -carbazole), 7.2 (m, 2H, -Ar-H), 7.2 (m, 1H, -carbazole), 6.8 (m, 4H, -carbazole), 5.3 (s, 1H, -OH), 4.1 (d, 2H, $J$ = 3, -OCH$_2$), 4.2 (m, 2H, -CH$_2$), 4.1 (s, 1H, -CH), 3.85 (s, 3H, -OCH$_3$), 2.92 (m, 2H, -CH$_2$), 2.9 (m, 2H, -CH$_2$), 2.1 (bs, -NH); MS: m/z (M$^+$+1) 407. 
Anal. Calcd for C$_{24}$H$_{26}$N$_2$O$_4$ (406.47): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.94; H, 6.48; N, 6.94 %.

Conclusion
In conclusion, an efficient, simple and convenient method for the preparation of pharmaceutically pure 1-(9$H$-carbazol-4-yloxy)-3-(2-(2-methoxyphenoxy)ethylamino) propan-2-ol, 5 (Carvedilol) via 2-(2-methoxyphenoxy)ethyl-4-methylbenzenesulfonate intermediate without formation of impurity-B by using weak base has been developed. This process is viable and very much suitable to prepare in bigger quantities.

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References